PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: (11) International Publication Number: WO 98/13485 C12N 15/00, C12Q 1/68 A1 (43) International Publication Date: 2 April 1998 (02.04.98) (21) International Application Number: PCT/US97/17302 (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, (22) International Filing Date: GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, 26 September 1997 (26.09.97) LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, (30) Priority Data:

US

(71) Applicant (for all designated States except US): MAXYGEN, INC. [US/US]; 3410 Central Expressway, Santa Clara, CA 95051 (US).

27 September 1996 (27.09.96)

(72) Inventors; and

60/037,742

(75) Inventors/Applicants (for US only): STEMMER, Willem, P., C. [NL/US]; 108 Kathy Court, Los Gatos, CA 95030 (US). VAN ES, Helmuth, H., G. [NL/NL]; Bandholm 89, NL-2133 DJ Hoofddorp (NL).

(74) Agents: SMITH, William, M. et al.; Townsend and Townsend and Crew LI.P, 8th floor, Two Embarcadero Center, San Francisco, CA 94111 (US). BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, I.C. LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, MI, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS FOR OPTIMIZATION OF GENE THERAPY BY RECURSIVE SEQUENCE SHUFFLING AND SELECTION

(57) Abstract

The invention provides methods of evolving nucleic acids for use in gene therapy by recursive sequence recombination. Many of the methods evolve vectors, both viral and nonviral, to have improved properties. For example, vectors are evolved to have improved properties of viral titer, infectivity, expression of a gene within a vector, tissue specificity, viral genome capacity, episomal retention, lack of immunogenicity of the vectors or an expression product thereof, site-specific integration, increased stability, or capacity to confer cellular resistance to microorganism infection. The invention further provides an isolated O6-methylguanine-DNA methyltransferase (MGMT) enzyme.